

## INFERTILITY AND ENDOMETRIOSIS

(Clinical Study of 37 Cases at M.C.K.R. Hospital)

(A Prospective Study of 5 Years)

by

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### SUMMARY

Diagnostic Laparoscopy has doubled the incidence of Endometriosis in infertile patients. Medical treatment with newer drug Danazol in low doses of 200-400 mg/day for 3-6 months is more effective than progestin therapy in mild to moderate cases of Endometriosis. Conservative Surgery in moderate to severe cases followed by Danazol also improves the pregnancy rate. A high corrected pregnancy rate of 62.5% was encountered in this series. 80% of the pregnancy patients had the infertility duration of not more than 5 years and all except 2, were below 30 years of age. Side effects with danazol are dose related-commonest being weight gain of above 4 kg (21.7%), mild irregular vaginal bleeding (26%) and amenorrhoea (73%). 70% of cases conceived within 6 months after the stoppage of therapy. Hence after 6m-1 yr of observation period a re-look Laparoscopy should be instituted to select the cases for fertility enhancement by conservative surgery.

### *Introduction*

Endometriosis is one of the most common cause of infertility in women older than 25 years. It increases the incidence of infertility to almost twice that in general population. It is seen in one third of the laparotomies done for infertility. Currently endometriosis has been diagnosed more frequently due to increased clinical

awareness and diagnostic endoscopy done in each case of long standing infertility. Conservative surgery along with the newer drug Danazol has made a significant advance with improved results in the management of Endometriosis in infertile women.

### *Material and Methods*

A clinical study of 37 infertile patients with endometriosis diagnosed by laparoscopy and/or laparotomy was done from

January 1982 onward. A complete infertility work up was done in each case. Duration of infertility and other associated infertility factors were noted down. Cases were grouped according to Acosta *et al's* classification. The preferred treatment in mild to moderate cases was surgical laparoscopy (wherever indicated) followed by a course of Danazol in low doses of 200-400 mg/day for 3-6 months depending upon the severity of symptoms and lesions. After a course of Danazol patients were instructed to avoid conception until one menses of normal length and flow had occurred. Conservative surgery in the form of excision of large tumorous lesion or to restore tubal function or anatomical correction of reproductive organ was done whenever needed followed by a course of Danazol in all for 2-3 months. A course of Danazol was also given in few cases before undergoing conservative surgery. The subjective and objective improvement, side effects with Danazol, pregnancy rate and its outcome were noted down during the follow-up of these cases till date.

#### Observations

There were 26 (70.3%) cases of primary infertility and 11 (29.7%) of secondary infertility. 67.5% of the cases were in the age group of 21-30 years and 32.5% were above 30 years. The oldest patient was 39 years.

There were 13 cases of mild, 8 of moderate and 5 of severe endometriosis in primary infertility. Four cases each of mild and moderate and 3 cases of severe endometriosis were present in secondary infertility.

The duration of infertility in these cases is depicted in Table I. 78.4% of the cases had the infertility duration of more than 2 years. The successful outcome in infertile

TABLE I  
Duration of Infertility

Duration in years	No. of patients
2 years	8
2-5 years	18
More than 5 years	11

patient with endometriosis is related not only to the management of this disease but also to other co-existing infertility factors. Table II shows the various asso-

TABLE II  
Associated Infertility Factors

Infertility Factors	No. of patients
1. Male Factors	4
Oligospermia	3
or	
Azoospermia	1
2. Chronic Pelvic Inf. Disease	8
Patent Tubes	5
Blocked Tubes	3
3. Uterine Myoma	9
4. Hormone Imbalance	4
Cystic Hyperplasia	2
Polycystic Ovary	2
5. Tubal Factor (Blocked Tube)	13
6. Combined	4

ciated infertility factors observed in our cases. Thirty patients were diagnosed endoscopically and various endoscopic operative surgery, done in these cases are depicted in Table III.

TABLE III  
Operative Laparoscopy Procedures

Laparoscopy Procedures	No. of patients
Fulguration of Endometriotic Nodules	10
Adhesiolysis and Fimbriolysis	8
Multiple Puncture of Ovary and or Ovarian Biopsy	6
Puncture, Aspiration of Small Endometriotic Cyst & Cauterization of End	5



Conservative surgery in the form of excision of large tumorous lesion to restore the tubal function for fertility enhancement or for pain control was done after diagnostic laparoscopy in 4 patients and directly in 7 patients. Two patients also had the surgical intervention after a course of Danazol-one for fertility enhancement and other for recurrence of disease.

Conservative surgery was done in the form of myomectomy in 6, unilateral salpingo-oophrectomy in 6 with or without ovariectomy or partial oophrectomy, adhesiolysis and fimbriolysis in 9 along with fulguration of endometriotic nodule and resection of endometriosis in 6 cases depending upon the extent of lesions.

Medical treatment mainly comprising of Danazol was given to 23 patients in total, out of which 15 had only Danazol; rest had other progestins before or after Danazol mainly because of the cost factor of this drug. Fourteen patients had only progestins for the same reason. The usual side effects encountered are shown in Table IV. Amenorrhoea was experienced by majority of patients while on medication. Mild vaginal bleeding at irregular interval was noticed at the lowest dose of 200 mg/day. Hoarseness of voice was complained by 2 patients who had 400 mg/day of the Danazol for 6 months. None of the patients

TABLE IV  
Side Effects With Danazol

Side Effect	No. of patients
Nausea	8
Mild Vaginal Bleeding	6
Weight Gain Over 4 kg.	5
Acne	4
Hoarseness of Voice	2

noticed decrease in breast size and hirsutism in our series.

Ten patients were lost to follow-up immediately after the diagnosis was made.

Considerable lessening of the objective findings were noted in 72% (out of 27 patients) and subjectively all women reported a considerable lessening of the symptoms of dysmenorrhoea, dyspareunia and pelvic pain.

Recurrence of disease after 3 years was noticed in 1 case. Marked reduction in residual disease was observed in 2 cases during the 2nd look laparoscopy.

A high pregnancy rate of 37% (uncorrected) and 62.5% (corrected) was observed in our series. Tables V and VI depict the correlation of pregnancy and its outcome with the severity of lesion, duration of infertility and interval period during which conception occurred after stopping the therapy.

TABLE V  
Pregnancy Rate

Total No. of pregnancy	10					
Uncorrected pregnancy rate	37%					
Corrected pregnancy rate	62.5%					
Duration in month after stoppage of therapy	No. of pregnancy					
	Prim. inf. (6)				Sec. inf. (4)	
	Mild	Mod	Severe	Mild	Mod	Severe
Upto 3 m.	1	1	—	1	—	—
3-6 m.	2	1	—	—	—	1
6-12 m.	—	1	—	—	2	1
After 1 Yr.	—	—	—	—	—	—

TABLE VI  
Outcome of Pregnancy

Duration of infertility in Yrs.	Severity of lesions	Outcome of pregnancy					
		Abor-tion	Con-tinue	Full term	Abor-tion	Con-tinue	Full term
2 Yrs.	Mild	—	1	—	—	—	—
	Moderate	—	—	—	—	—	1
	Severe	—	—	1	—	—	—
2-5 Yrs.	Mild	—	1	1	—	1	—
	Moderate	—	—	—	1	—	(SB)
	Severe	—	—	—	—	—	—
More than 5 Yrs.	Mild	—	—	—	—	—	—
	Moderate	—	1	1	—	—	1
	Severe	—	—	—	—	—	—

Out of 10 pregnant patients, 7 had conceived after Danazol—in 2 cases Danazol was given after taking other progestins. Three patients had conception after pseudo-pregnancy regime. Only 1 case had conceived after conservative surgery and in rest all medical treatment was effective.

#### Discussion

Since the last decade Danazol has made a significant evolution in the medical management of endometriosis in infertile subjects. There is still much controversy regarding the use of Danazol. Various studies had already suggested the improved efficacy of Danazol over progestins when used alone in mild to moderate cases of endometriosis (Wheeler and Malinak 1981; Butteram *et al* 1982 and Barbieri *et al* 1982). Pre-operative use of Danazol facilitates surgical removal of disease and reduces post-surgical adhesions in severe endometriosis (Butteram *et al* 1982; Barbieri *et al* 1982 and Kistner 1984).

Post-operative Danazol in severe endometriosis also improves the pregnancy rate (Wheeler and Malinak 1981). Kistner *et al* (1984) agree with the use of pre-operative use of Danazol but not with that of post-

surgical Danazol as they believe that after surgery the conception usually occur within 6 months. Surgical laparoscopy for releasing adhesions and for resection of endometrioma followed by medical treatment with Danazol is more effective in infertile subjects with endometriosis (Cohen 1980 Daniell and Christianson 1981).

The earlier major studies had employed a higher dose of Danazol (800 mg per day) but now all have agreed that even with a low dose of 400 mg/day, the same efficacy with minimal side effects can be achieved. (Biberoglu and Behraman 1981 and Kistner *et al* 1984).

In our study also, experience with Danazol in low doses has been excellent. A major benefit of this schedule being the reduction in the total cost of a course of Danazol.

A high corrected pregnancy rate (62.5%) and uncorrected one (37%) were observed in our cases; similar to those observed by others. The pregnancy rate recorded vary from 40.6% (Greenblatt 1974) to 72.2% (Dmowski and Cohen 1978). Daniell and Christianson (1981) had the pregnancy rate of 68%. Kistner *et al* (1984) found the pregnancy rate in mild cases without any associated infertility



factors to be 50.8% with Danazol or pseudo pregnancy therapy. Pregnancy rate subsequent to surgical treatment of ovarian endometrioma was 76% without any adhesion and with adhesion and pelvic involvement it was only 35%.

Acosta (1973) and associates observed the highest pregnancy rate after surgery in patients with 1-3 years of infertility (57%) and lowest rate (25%) in patients with 4-5 years of infertility their pregnancy rate in mild endometriosis was 75% moderate 50% and severe 33%.

In our series all the pregnant patients except one had undergone only surgical laparoscopy. Other associated infertility factors were present in 4 cases in the form of myoma in 2, oligospermia and cervicitis in 1 and inflamed tubes in 1. The peritubo-ovarian adhesions was present in 2 cases—one case each of moderate and severe endometriosis.

In 3 cases conception had occurred after sex steroids and in 7 after Danazol (2 out of 7 cases had been already given other progestins but pregnancy occurred only after Danazol). This shows the high efficacy of Danazol over progestins in our cases.

Eighty per cent of the pregnant patients in our series had the infertility duration of not more than 5 years and except the 2 all were below the age of 30 years. This again suggests that, pregnancy rate in endometriosis is affected by the age of patient and duration of infertility. According to Kistner (1975) several factors like age above 35 and infertility duration of more than 5 years also lowers the pregnancy rate by 25-30%.

No increase in incidence of spontaneous abortion was noticed in our cases (only one had 1st trimester abortion). One had a full term still birth but there was associated myoma and cord around the neck

of the foetus in that case. Daniell and Christianson (1981) and Kistner *et al* (1984) did not notice any increased incidence of spontaneous abortions while Dmowski and Cohen (1978) had reported an increase in second and third trimester fetal wastage.

Seventy per cent of our cases conceived within 6 months after the stoppage of therapy. Dmowski and Cohen (1978); Daniell and Christianson (1981) and Kistner *et al* (1984) had reported the same.

Three of our patients conceived after giving ovulatory drugs. This again confirms the association of the ovulatory drugs function in endometriosis.

Minimal side effects were observed as they are stated to be dose related. They were in the order of frequency: (i) Nausea in 8, (ii) irregular mild vaginal bleeding in 6 (iii) Weight gain of more than 4 kg in 5 and (iv) Acne in 4.73% had amenorrhoea during the course. None of the patients in our series discontinued the drug because of its side effects.

Barbieri *et al* (1981); Buttram *et al* (1982) and Kistner (1975) had reported side effects with Danazol in 85% cases (at a higher dose of 800 mg/day); major being weight gain, edema and decrease in breast size. The fewer side effects observed in our cases may be due to low dose of Danazol used.

Relook laparoscopy to assess the effectiveness of the therapy was not possible in our cases as our patients are not agreeable to undergo the same. Effectiveness of the therapy was only assessed by the improvements in the subjective and objective findings in them.

#### Conclusion

1. Surgical laparoscopy followed by Danazol is an effective treatment in mild

to moderate cases of endometriosis with infertility.

2. The high efficacy with low dose of Danazol in the treatment of infertility associated with or due to endometriosis has been observed similar to that documented with a higher dose. A high pregnancy rate of 67% (corrected) was noted with Danazol in lower doses in our cases.

3. The age of patient and duration of infertility affect the pregnancy rate but there is not much correlation with the severity of lesions as noticed in our cases.

4. The response of the patient with Danazol is variable as is the dosage requirement. Hence the regime of 200 mg/day should be the lowest possible treatment dosage to be increased up to 400 mg/day for 3-6 months according to subjective and objective improvement.

5. Fewer side effects are noticed as they are dose related and due to mild androgenic and hypoestrogenic effects of the steroid.

6. Most of the conceptions occurred within 6 months after stopping the therapy. Hence after 6 months—1 years of observation period, a relook laparoscopy should be instituted to select the cases for fertility enhancement by conservative surgery and also to assess the effectiveness of the

therapy. This will prevent unnecessary delay in surgery where fertility enhancement can be done.

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